Vigilance - News

June 2010

In this Newsletter:

I: Editorial

Review of surveillance of pandemic influenza

This past winter, the Vigilance Unit conducted intense surveillance activities to monitor suspected adverse events following immunization against pandemic (H1N1) 2009 influenza. Swissmedic, together with *the* Uppsala Monitoring Centre, developed a publicly accessible online form available to physicians and pharmacists called “PaniFlow®” to report directly cases of suspected adverse events following pandemic influenza vaccination. PaniFlow® remained online until 31 March 2010 and registered more than 500 reports. There is no “due date” to report a suspected adverse event following immunization or to provide further follow up information on a registered case. Swissmedic welcomes and continues to receive information through the usual reporting mechanism with forms submitted through the 6 regional pharmacovigilance centres in Basel, Bern, Geneva, Lausanne, Lugano and Zurich.

The Vigilance Unit prepared and published regular interim surveillance reports and a Final Report on safety of vaccines against pandemic (H1N1) 2009 influenza. A public version of the Final Report will be released. A second version of the Final Report, which included more detailed clinical descriptions (still maintaining strict confidentiality, with patient and reporter identifiers removed), is under review by experts in the Swissmedic Human Medicines Expert Committee (HMEC) in July 2010. Conclusions from the HMEC will be published.

Several valuable lessons were learned from the experience with PaniFlow®. The value of an electronic reporting form was well demonstrated, and permitted real-time analysis of newly licensed and widely used medicinal products. Swissmedic’s telephone hotline for using PaniFlow®

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was important for user support such as login questions as well as providing immediate user feedback. The online PaniFlow® system was also welcomed by most reporting pharmacists and physicians. Swissmedic recognises the safety surveillance of pandemic influenza vaccines in Switzerland was made possible by the clear engagement and contributions of health professionals. With the positive response to PaniFlow®, Swissmedic Vigilance is exploring the expansion of electronic reporting of suspected adverse drug reactions for other medicines, as an alternative in the near future to the current system of Yellow Card forms. The ease of use of and access to an electronic reporting system are important considerations.

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II: Flash: Signals relating to the safety of medicines from the Swiss database of the Vigilance Unit

PHARMACOVIGILANCE:

Sibutramine - cardiovascular risk: Suspension of authorisation in the EU and in Switzerland

Reductil®, the only product containing sibutramine in Switzerland, was authorised in Switzerland in January 1999. From the beginning, Reductil® was the subject of special monitoring during the clinical trials because of its central adrenergic characteristics with increased heart rate and blood pressure. As commissioned by the European Medicines Agency (EMA), the pharmaceutical company Abbott carried out a comprehensive long-term trial: "SCOUT" (Sibutramine Cardiovascular OUTcome Trial). Following several intermediate reports, the authorisation holder informed Swissmedic for the first time of the final results from SCOUT in November 2009.

Patients treated with sibutramine had a higher risk regarding the primary outcome event which was defined as the sum of the following events: non-fatal myocardial infarction, non-fatal cerebrovascular accident, reanimation after cardiac arrest or death related to cardiovascular causes (561/4906, 11.4%), compared with patients taking a placebo (490/4898,10.0%); Hazard ratio 1.162 (95% CI 1.029, 1.311); p=0.015. There was no significant difference for the secondary outcomes of all-cause mortality and death from cardiovascular causes alone. The first results showed a statistically significant risk for the primary outcome events, which triggered a safety investigation initiated by Germany in the EU ("Article 107 referral") for all products with sibutramine as the active substance.

On 21 January 2010, the EMA recommended to the European Commission that the authorisation for all EU countries should be suspended; according to the results of the SCOUT study there was no longer a positive risk-benefit ratio. The US Food and Drug Agency (FDA) simultaneously informed the public that as a result of the SCOUT study, the active substance sibutramine should not be immediately withdrawn from the market, instead the Product Information should be adjusted by including new contraindications on cardiovascular diseases and a new restriction on the treatment duration of up to one year for responders and three months for non-responders. All these new restrictions in the USA were already fully included in the Product Information in the EU and, to a near full extent, in Switzerland.

SCOUT was a randomised, placebo-controlled, double-blinded study with approximately 4,900 patients per group in parallel comparison followed over a period of up to six years. During the six-week introductory period, all patients were given sibutramine. The study was commissioned by the EMA, which also gave its approval to the study design. The fact that the overall total of primary outcome events (POEs) was well below expectations led to the trial being extended well beyond its originally planned duration. This indicates a significant effect of the trial that had originally not been fully clarified, i.e. that independent of the treatment group, the cardiovascular risks in the trial setting were clearly reduced. Most of the patients recruited to the SCOUT trial should not have been treated with the product, according to the authorised Product Information in Switzerland and the EU, since they had cardiovascular risks or diseases listed as contraindications. It is also important that only a limited treatment time was authorised in the Product Information.

Based on the results of the SCOUT study, Swissmedic also considered the risk-benefit ratio was no longer positive, and on 28 January 2010 initiated investigatory procedures. The main reason was the significant findings of increased cardiovascular risk using a prospectively defined primary outcome event, and given the relatively low benefits. It should

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also be noted that events which normally would have been avoided as a result of weight loss occurred more frequently while under sibutramine in the SCOUT trial. The company's opposing position was above all based on the fact that the treatment duration (up to 6 years and no cessation after three months for non-responders) and that the high-risk population in SCOUT did not correspond to the authorisation status and at the same time, post-hoc analysis for sub-groups and at earlier points were favourable for sibutramine. However, it is by no means clear what would be the benefits even for responders with a treatment limited to one year (as prescribed in the EU), when considering the long-term course of obesity and comorbidities.

After review of the submitted documentation and statements, Swissmedic issued a formal decision to suspend the marketing authorisation. Through a Healthcare Professional Communication and publication, the prescription and dispensation of Reductil® was banned as of 30 March 2010 until further notice.

The legal terms *suspension* and *revocation* of an authorisation should be explained here. The *suspension* of an authorisation constitutes the less intervening measure, and is reversible if and when the authorisation holder succeeds in invalidating the concerns leading to this measure and can prove a favourable risk-benefit ratio for the indications that continue to be claimed. However, if a company wishes to place a product back on the market for which authorisation has been *revoked,* a new application for authorisation is required.

Progressive multifocal leucoencephalopathy (PML) – update from Swissmedic's position

The increasing number of reports relating to PML could lead to assumptions that this disease is either a new or a rapidly increasing problem, but neither is correct.

Already published as an phenomenon in 1958[1], PML was described very early in German-speaking countries, in recipients of kidney transplants with immunosuppression (1977), in patients with haemophilia A infections (1985), and in connection with Sharp's syndrome / mixed connective tissue disease (1991). In the 1990s, HIV infection was associated with nearly 90% of the several hundred deaths attributed to PML in the USA. In recent years, PML cases have mainly occurred during treatment with new biological medicines / monoclonal antibodies. The significance of marked immunosuppression was already then recognised as a risk factor.

Active substances associated with PML:

Efalizumab (Raptiva®):
The active substance indicated for severe, chronic plaque psoriasis was on the market in the EU and Switzerland for four years. Following its authorisation, the substance's overall immunosuppressive effect was revealed as being more significant than initially presumed and corresponding general warnings already became more stringent before the first case of PML was reported. In February 2009, the active substance was taken off the market in the EU and Switzerland, triggered by three confirmed cases of PML from abroad.

Rituximab (MabThera®):
The active substance indicated for non-Hodgkin's lymphoma and rheumatoid arthritis (monoclonal chimeric antibody against CD20, causing cell lysis of B-lymphocytes) is linked

[1] Astrom KE, Mancall EL, Richardson EP Jr.: Progressive multifocal leuko-encephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. *Brain* 1958; 81: 93-111.

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to several confirmed cases among a total of about two dozen reports of PML. In November 2009, information was provided on the Swissmedic website and by means of a Health Professional Communication (HPC), highlighting PML reports related to patients with rheumatoid arthritis.

Alemtuzumab (MabCampath®):
The monoclonal antibody (Anti-CD52), which also causes cell lysis of lymphocytes and is authorised for treating chronic B-cell leukaemia, has led to about 10 confirmed cases of PML, with others that are suspected but not confirmed.

Natalizumab (Tysabri®):
Among its other properties, Natalizumab restricts the adhesion of mononuclear leucocytes and their migration to inflamed tissue. It is authorised for treatment of multiple sclerosis (MS) and the known increased risk of developing a PML (listed in the Product Information) applies almost exclusively to MS patients. At present, and unlike in previous years, there has been a clear increase in the number of recorded cases of PML. In conjunction with the manufacturer, Swissmedic is investigating the extent to which this constitutes a net increase. Aspects to be taken into account are the latency (time until the onset of PML), the duration of the treatment, the increase in patient exposure worldwide (market penetration), polytherapy, increased awareness and improved diagnosis.

Other medicines:
The list is not exhaustive. Other immunosuppressive agents often taken as combined therapy, e.g. mycophenolate, have been linked to PML.

On PML:

According to the ICD-10 coding A 81.2, PML is in the same group as Creutzfeldt-Jakob disease and subacute sclerosing panencephalitis. The cause of PML is considered to be John Cunningham virus (JCV), a virus which was named after the patient. The pathogenesis leading to the development of PML nevertheless requires a series of phases[2]. Some 80 to 90 % of the population are, or have been, infected with the JCV but are asymptomatic. To date, it has not clear whether PML is a result of the primary infection. Current thinking favours persistent infection or the reactivation of latent, existing JCV infection.

Clinical aspects:
Presents with weakness and cognitive loss. Also frequent are cephalgia, difficulty in walking, in speaking, and problems with vision. Differentiating PML from the primary disease of multiple sclerosis is difficult. It is reasonable that considerable time may pass before PML is suspected.

Histopathological aspects:
Triad of demyelinisation, abnormal oligodendroglia nuclei under electron microscopy and giant astrocytes.

Imaging:
Typical are hypodense lesions in affected white matter on CT scan, which can closely resemble MS. MRI scan can estimate the neuron loss and demyelination.

Investigation of cerebrospinal fluid:
The investigation of cerebrospinal fluid is essential for a diagnosis by exclusion. Moreover, evidence of the JCV and the amplification with PCR (polymerase chain reaction), linked to clinical and radiological characteristics, are considered sufficient for confirming the diagnosis.

Differential diagnosis:
For MS patients, a new phase of the disease should above all be considered. For AIDS patients, an HIV encephalopathy or a CNS infection with common pathogens should be ruled out. For other patients, a differentiation should be made from PRES (posterior reversible encephalopathy syndrome), which has a shorter duration and regression of symptoms. PRES has been linked, among other factors, to immunosuppressive medica-

[2] Berger JR. Progressive Multifocal Leukencepholopathy. *Current Neurology and Neuroscience Reports* 2007; 7: 461-469.

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tions, cytokine therapy and endothelial growth factor inhibitors.

Therapy:
There is no specific antiviral active substance against the JC virus. The therapy depends on whether patients are HIV positive or have received organ transplants. For patients with MS, rapid intervention in the form of plasma exchange has led to a certain degree of success.

Prognosis:
Recently, the average survival time has increased by many months. Even though some patients have lived for many years following the diagnosis of PML, the prognosis is usually very poor.

Where do reference laboratories exist?
For Switzerland, the company Biogen-Dompé is recommended as the agent for these specialised laboratory services.

In Germany, the reference laboratory is the Würzburg University Institute for Virology and Immune Biology.

In the USA, the reference laboratory is the NIH (National Institutes of Health).

Neurology associations:
At present, to the extent of our knowledge, there are no generally available position statements or guidelines established by neurological societies.

Conclusion:

PML raises numerous scientific questions. Confirmation of diagnosis should take place at established centres. Therapy is based on the primary disease. No official guidelines yet exist. Like other national authorities, Swissmedic is monitoring the development of PML in connection with various products extremely closely. This rare but very severe disease, which usually arises in conjunction with marked immunosuppression, can also be triggered by medicines that are used for life-saving measures or for extremely severe illnesses. Together with their strict indications for use, treatment with these medications requires regular assessment, patient information, and careful monitoring (for Natalizumab®, for example, there is a special risk management programme).

Formal investigation for combined oral contraceptives (COC) containing drospirenone closed - updated Product Information for Prescribers and Patients

The Product Information for Prescribers and Patients for combined oral contraceptives (COC) containing drospirenone (Yasmin®, Yasminelle® and YAZ®) has been updated and reflects the latest information and warnings about the risk of venous thromboembolism (VTE). The most important updates concern:

- Updated numbers regarding absolute VTE-risk for COC-users in general, for non-users and for pregnant women.
- Relative VTE-risk under COCs containing drospirenone in comparison with second-generation COCs (with levonorgestrel) and third-generation COCs (desogestrel or gestodene).
- Increased VTE-risk after restarting a COC following a pill-free interval of 4 weeks or more.
- Clearer presentation and detailed description of the warning symptoms of VTE.

The new texts were published online at the end of April 2010 (http://www.documed.ch/). The current updates match the results of the broad investigation of the VTE-risk associated with hormonal contraceptives about which Swissmedic had informed healthcare professionals and the public in October 2009[3]. The formal investigation for COCs containing drospirenone opened in August

[3] De Geyter C, Meier CR, Pavelic Ferretti D, Kwan HY, Stoller R. Venous thromboembolism and combined oral contraceptives – current situation. Published in: pharmaJournal 2009;21:4-6 [in Ger. and Fr.], *Schweizerische Ärztezeitung* 2009;43:1654-1657 [in Ger. and Fr.], Swissmedic Homepage 22.10.2009

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2009 has now been closed with the update of the Product Information.

Extracts of the section “Warnings and precautions for use” of the updated Product Information for prescribers of Yasmin®, Yasminelle® und YAZ® concerning VTE-risk are presented on the Swissmedic Homepage, in the pharmaJournal and in the *Schweizerische Ärztezeitung*[4].

[4] Swissmedic closes the formal investigation for contraceptives containing drospirenone. Published in: pharmaJournal 2010;9:13-14 [in Ger. and Fr.], *Schweizerische Ärztezeitung* 2010;17:671 [in Ger. and Fr.], Swissmedic Homepage 25.03.2010

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III: International activities

International Pharmacovigilance cooperation: Update on processes of the "International Pharmacovigilance Work-Sharing Group" (IPWG)

Within the framework of international collaborations in pharmacovigilance, contacts at the highest levels among the regulatory authorities in Australia (Therapeutic Goods Administration, TGA), Canada (Health Canada), Singapore (Health Science Authority, HSA) and Switzerland (Swissmedic) were formalised in May 2008 in the form of Memoranda of Understanding (MoUs). The objective of the MoUs was to build up a network of mutual information exchange and work-sharing.

In Switzerland, pharmacovigilance cooperation is entrusted to Swissmedic's Safety of Medicines Division, which is responsible for taking all initiatives in this collaboration. A Working Group, the "International Pharmacovigilance Work-Sharing Group", or IPGW, was created with the following areas of responsibility:

- identifying and comparing pharmacovigilance procedures in each country, and
- publishing the work by each agency, which in return may monitor or take part in work carried out by other group members

An Internet platform on a dedicated website was made available by WHO (MedNet) in order to facilitate the exchange of documents. In addition, quarterly telephone conferences unite the departmental heads in charge of pharmacovigilance and their staff in each country in order to discuss current topics and take the necessary decisions.

During the four first telephone conferences organised by Health Canada between July 2008 and July 2009, the focus was on the numerous obstacles to full collaboration and problems to overcome major structural and procedural differences, such as:

- the levels of scientific expertise and experience in each agency
- the priorities of each agency and the absence of common interest on specific topics
- the fact that the control and review methods depend upon national legislations leads to major difference in interpretations regarding objectives and comprehensive approach to the work conducted
- the resources allocated (human and material): English translation prior to the exchange of documents is essential for Swissmedic

Status and forecast

This first year of functioning has permitted the IPWG to take stock of challenges it had to face. The following results were achieved:

- the framework conditions for the cooperation have been established (Terms of Reference for the group, teleconferences, MedNet)
- the platform for exchange is working to the satisfaction of its users
- signals and Patient Safety Update Reports (PSURs) evaluations have been exchanged

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Although the exchanges of signals are occurring, their form and their traceability must be improved in order to ensure compatibility and ease of use by each country member of the IPWG. As of May 2010, they will be updated regularly (on a monthly basis).

Although not all of the PSUR evaluations can be published online, we shall make a selection of documents available to the group members, as well as analysis of certain sensitive products that has been conducted and translated into English.

After a pause of several months that can be attributed to the influenza (H1N1) 2009 pandemic, which required significant resources, the IPWG is now embarking on an additional step towards sharing tasks. The next step will consist of adapting and updating agency procedures and training the staff members who will be applying them, with expected completion by the end of 2010.

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IV: Statistical review 2009

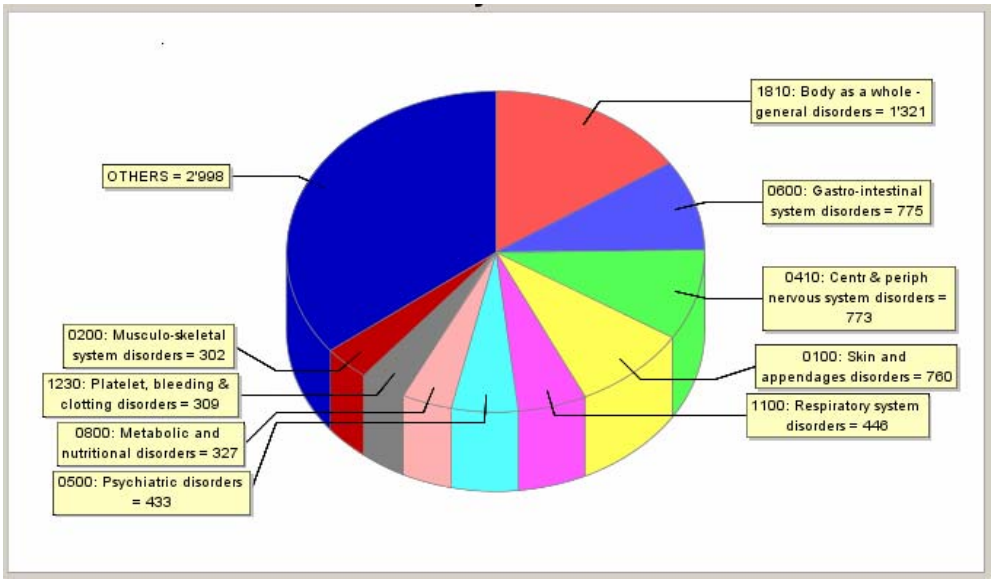
VIGILANCE OF HUMAN MEDICINES:
Review 2009
Descriptive statistics of adverse drug reactions (ADRs) in Switzerland

1. Adverse Drug Reactions* (ADRs) Reports stratified by System Organ Class (SOC) and Seriousness

During the period from January to December 2009 (datalock 27 April 2010), Swissmedic entered 4914 reports into its national ADR database (Not included in this analysis are the ADR reports still being processed and the ADR reports following vaccination against pandemic (H1N1) 2009 influenza that were collected and entered into a separate database).

An adverse drug reactions report contains at least one ADR mentioned, and on average there were three ADRs per report in 2009.

Diagram 1: Adverse Drug Reaction Case Reports by System Organ Class, 2009



As indicated in Diagram 1, of the 4914 reports most ADRs are classified under the following most frequent System Organ Classes (SOC/ WHO Adverse Reaction Terminology):

- Body as a whole – general disorders
- Gastrointestinal system disorders
- Central and peripheral nervous system disorders
- Skin and appendages disorders
- Respiratory system disorders
- Psychiatric disorders
- Metabolic and nutritional disorders
- Platelet/bleeding & clotting disorders
- Muscular-skeletal system disorders

All other ADRs were compiled in the group “Others” and are not further specified in detail.

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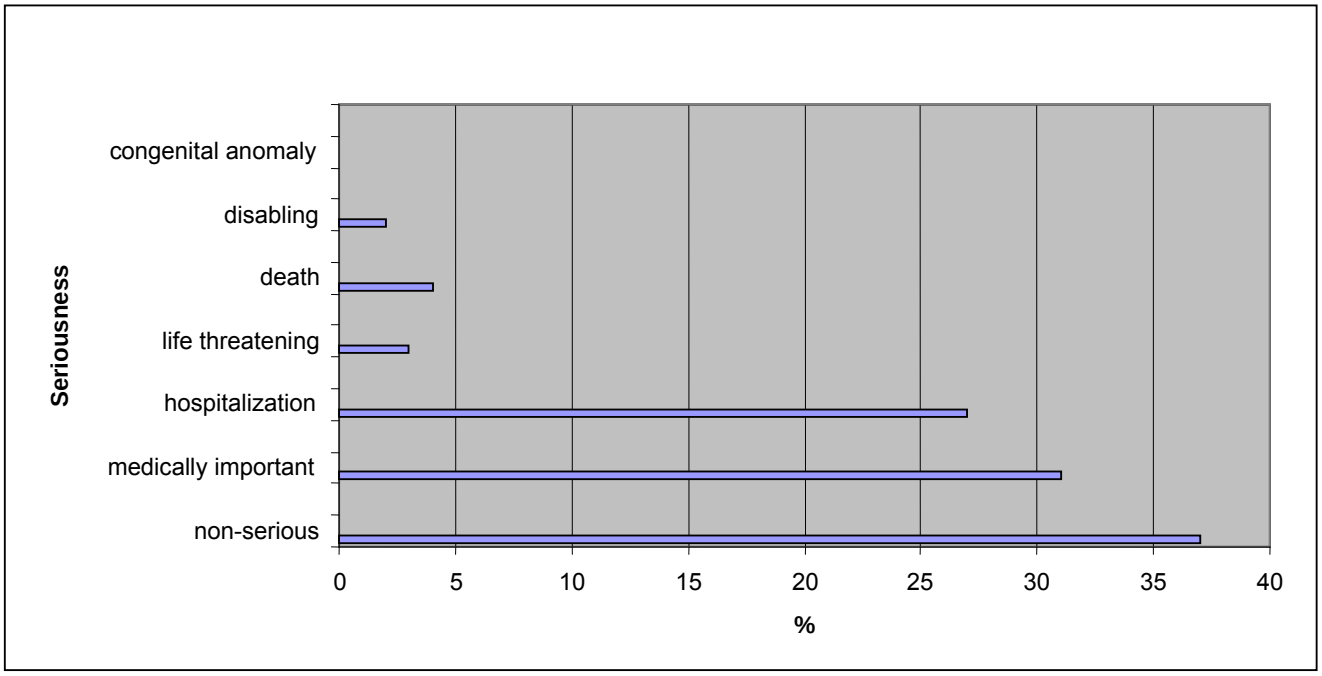
Diagram 2: Distribution of ADR case reports by seriousness, 2009



The distribution of the 4914 ADR case reports by seriousness is given in Diagram 2: 37% of the reports were considered non-serious, 31% were classified as other medically important condition and 32% as serious case reports (27% hospitalization, 3% life threatening, 2% disabling and 0.1% as congenital anomaly). 4% (n=191) of all reports had a fatal outcome with the following causality assessments: in 26% the fatal cases were considered to be drug related, in 58% the drug might have contributed to the fatal outcome and in 16% the fatal cases were classified as unrelated.

Note: It is important that one case report may include more than one seriousness criterion.

2. Adverse Drug Reactions Reports analysed by Seriousness and Labelling**

In 21% of all the ADR reports (n=1061), at least one serious ADR was considered as not consistent with the labelling mentioned in the Product Information. In about 20% of all reports (n=906), at least one non-serious ADR was considered as not labelled or not adequately labelled.

ADRs which are serious unlabelled or not adequately labelled are critical reactions which may lead to signals and related actions, such as the publication of “Healthcare Professional Communications”, or revisions of the Swiss Product Information, or other appropriate actions. The non-serious unlabelled case reports may also have consequences, such as changes to the Product Information.

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3. Adverse Drug Reactions Reports stratified by Gender, Age Group and Sender

- Out of the 4914 ADR reports received in 2009, 59% (n=2883) referred to female and 36% (n=1766) to male patients. For 5% (n=265) information on gender was missing.
- Almost three quarters (72%) of the case reports were adults/elderly, 4% adolescent/children, and 2% infants/neonates. In 22% the age was missing.
- 46% of ADR case reports were reported via regional PV Centres and 54% by pharmaceutical companies.

* *Source: The Swissmedic Pharmacovigilance Database*
** *Note: "Unlabelled" also includes "not adequately labelled" ADR*

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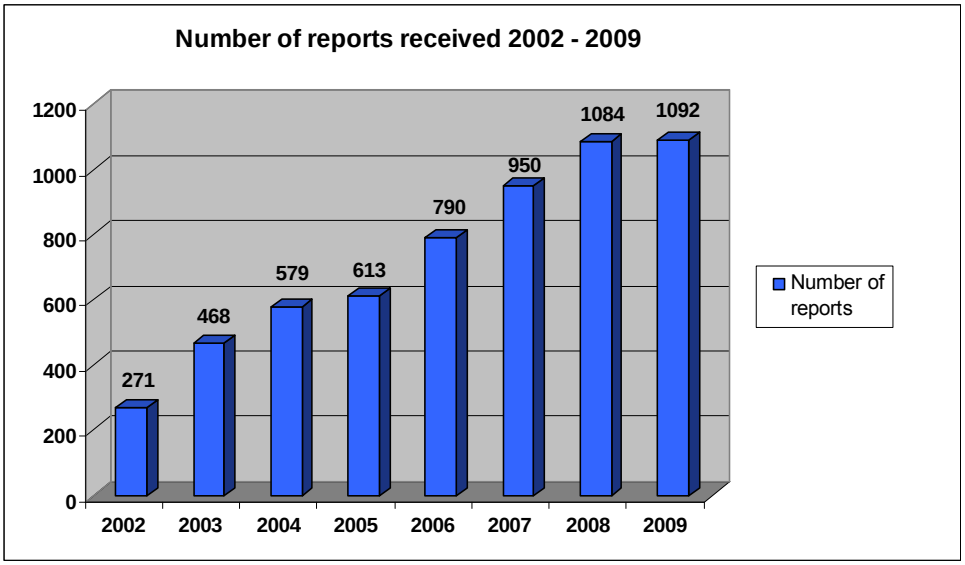
HAEMOVIGILANCE:
Review 2009

Haemovigilance (HV) signifies collecting, reporting, analysing and evaluating suspected adverse events associated with transfusion. The main purpose is to find answers to the following questions:

- What types of incidents occur?
- How frequent / dangerous are they?
- How do they happen?
- Which are avoidable?
- How can they be avoided?

This leads to possible measures to improve the quality and safety of transfusions as a contribution towards patient safety.

Figure 1



Reports received in 2009

Table 1: Number of haemovigilance reports 2009

Category	Number
Number of reports on adverse transfusion events	783
Number of events following transfusion	798
Number of IBPT (incorrect blood product transfused) reported	34
Number of Near Miss events reported	275
Total number of reports received	1092
Total number of events reported	1107

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In 2009, a total of 1092 haemovigilance reports were submitted to Swissmedic. 832 events following transfusion were described in 817 reports. In 15 cases, the report related to more than one event, e.g. a febrile non-haemolytic transfusion reaction (FNHTR) accompanied by symptoms of circulatory overload.

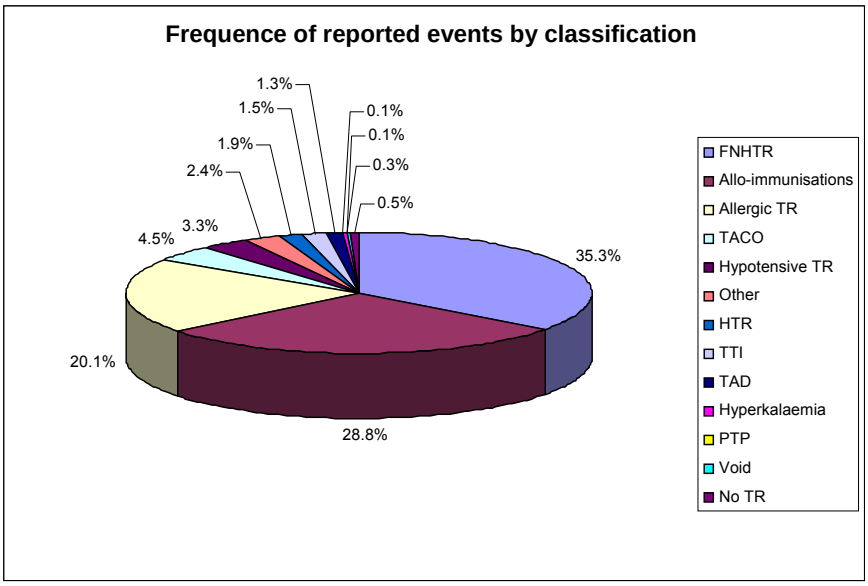
The reports of IBPT („incorrect blood product transfused“) and Near Miss events are recorded separately from transfusion reactions. 34 IBPT and 275 Near Miss events were reported in 2009, for which the latter corresponds to a 15% increase in the number of reports compared with the previous year.

Table 2: Number of events reported in 2009, by classification and frequency

Classification	Number of cases	%
Febrile non-haemolytic transfusion reaction (FNHTR)	282	35.3
Allo-immunisation	230	28.8
Allergic transfusion reaction	160	20.1
Transfusion associated circulatory overload (TACO)	36	4.5
Hypotensive transfusion reaction	26	3.3
Other	19	2.4
Haemolytic transfusion reaction (HTR)	15	1.9
Transfusion-transmitted infection (TTI)	12	1.5
Transfusion-associated dyspnoea (TAD)	10	1.3
Hyperkalaemia	1	0.1
Post-transfusion purpura (PTP)	1	0.1
Void (duplicate reporting)	2	0.3
Event not transfusion related	4	0.5
Total events	798	100.0

The table of reported transfusion reactions by classification and frequency shows no significant changes in the distribution of the various reactions in comparison with previous years. As in the past, the most frequently observed transfusion reactions are FNHTR, allo-immunisations and allergic reactions.

Figure 2



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In Switzerland, approx. 300,000 red cell concentrates (RBC), 70,000 units of fresh frozen plasma (FFP) and 25,000 platelet concentrates (PC) are transfused annually. The majority of transfusion reactions are related to RBC, corresponding to the greater number of RBC transfusions administered compared with other blood components. However for platelet concentrates, the rate of transfusion reactions (number of TR per 1000 transfused components) is roughly double that of RBC (1.26 for RBC; 2.7 for PC).

Figure 3

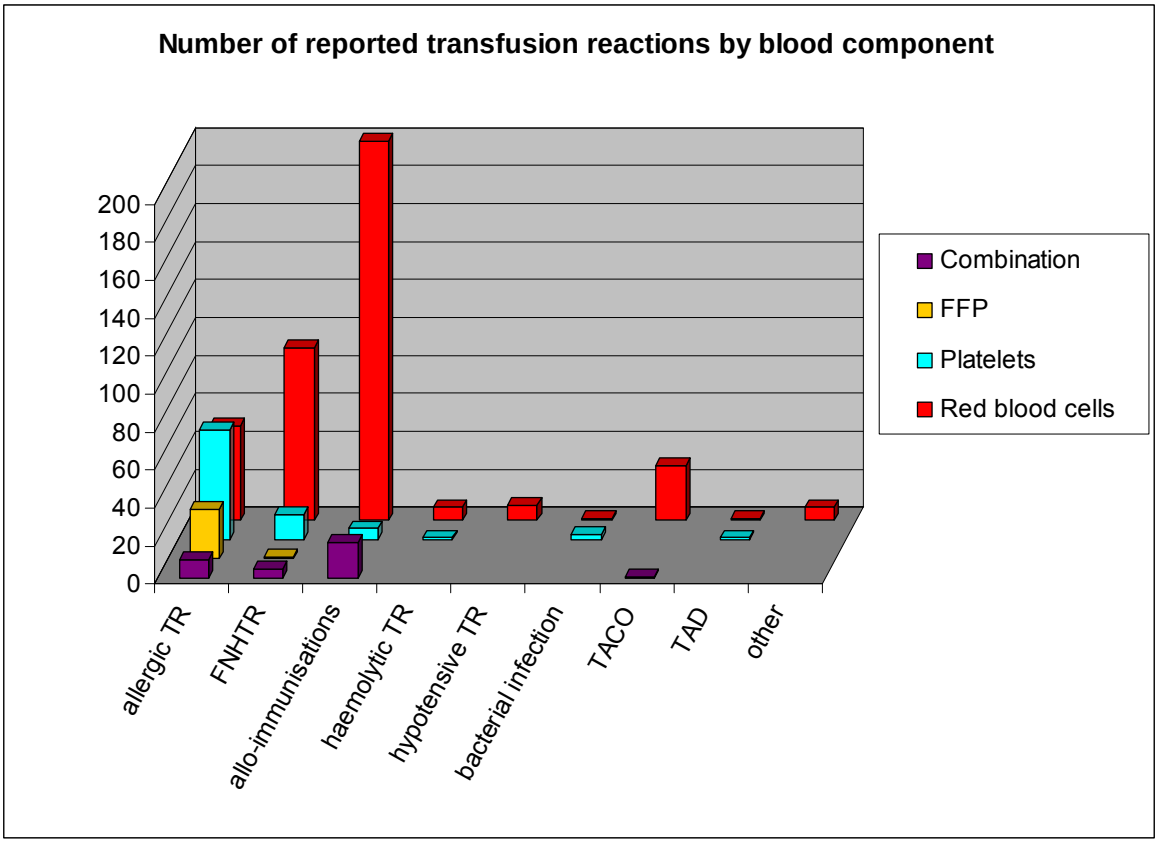
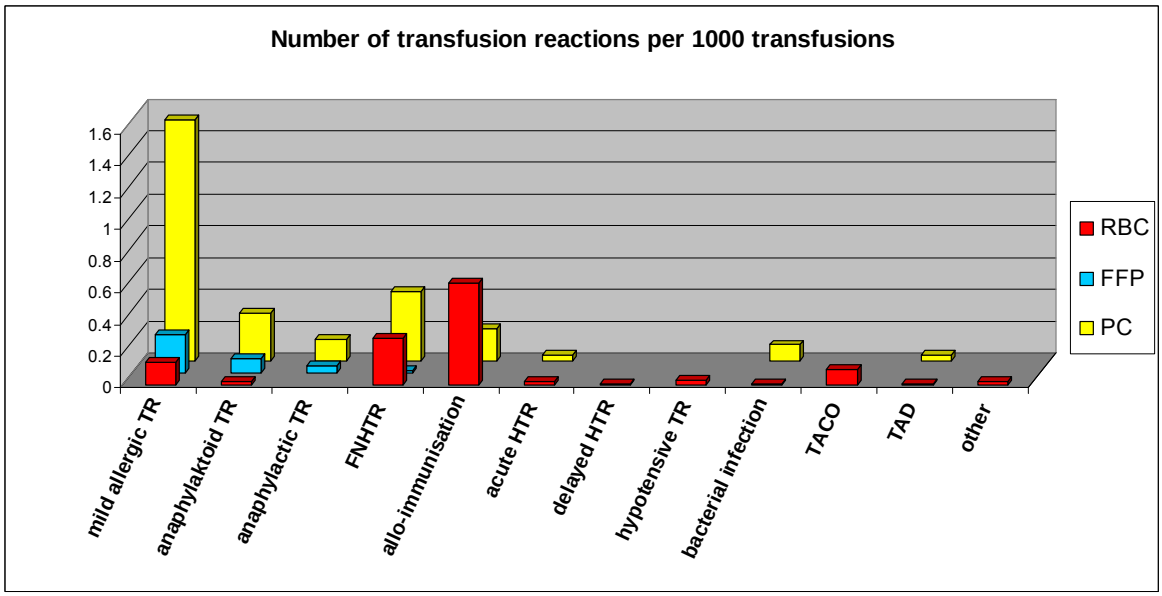


Figure 4



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The absolute number of reports of mild to medium allergic reactions was nearly equal for RBC and PC, even though platelet concentrates are administered about 10 times less frequently. Anaphylactic reactions were only reported in relation to plasma or platelet transfusions. Apart from one febrile reaction, the only reactions that occurred in the course of FFP transfusions were allergic reactions.

Three of the four transfusion-transmitted bacterial infections were caused by contaminated platelet concentrates. The introduction of pathogen-reduction methods into the manufacturing process of platelet concentrates is currently an ongoing project in Switzerland.

2009 was the first year without any reports of reactions that fulfilled the criteria for transfusion-related acute lung injury (TRALI). There were 5 suspected cases, but the investigations found that all were either belonging to a different classification or not transfusion related.

This year, the Swissmedic Haemovigilance team organised several workshops for haemovigilance officers, their collaborators and other healthcare specialists interested in haemovigilance. Seminars on topics such as “Introduction to haemovigilance” or “Haemovigilance case studies” were very well attended. On the 26th of August 2010 we will be hosting the 3rd Swiss Haemovigilance Seminar. Anyone interested in haemovigilance is cordially invited to participate!

Please find further information on the Swissmedic website under the following link:
http://www.swissmedic.ch/aktuell/00051/01249/index.html?lang=en

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VIGILANCE OF VETERINARY MEDICINES: Review 2009

A total of 134 vigilance reports relating to veterinary medicines were submitted. This represents about a 26% increase compared with 2008 (106 reports). Most of the reports (69; i.e. 52%) were collected by distributors or manufacturers under legally required pharmacovigilance activities and subsequently forwarded to Swissmedic. A further 45 (34%) of the reports were submitted directly by practising veterinarians. The remaining reports came from the Swiss Toxicological Information Centre in Zurich (11), from owners of animals (6) or various official entities (3).

Stratification by types of animals and categories of medicines

An overview by the types of animals is shown in Table 1. To a large extent, the distribution corresponds to that seen in recent years: dogs and cats together constitute the largest group with 65% of all reports (61 reports for dogs, 25 for cats). After this come cows / calves (30 reports; 23%), and horses and pigs with 4% each. Individual reports of adverse reactions in sheep and small rodents were also received, as well as in humans handling these veterinary medications.

An overview stratified according to the recognised ATCvet categories is shown in Table 2. Most of the reactions, as was the case in previous years, concerned the use of antiparasitics (40; 30%) and anti-infectives (26; 19%). These two categories constitute the largest groups of veterinary medicines authorised in Switzerland. For externally applied antiparasitics (collar and spot-on products), the reactions were mainly in the form of pruritus or reddened skin, and more rarely systemic (CNS symptoms such as lethargy, ataxia, tremors and cramps). In most cases, the symptoms disappeared when treatment was stopped. Regarding the anti-infectives, many cases concerned allergic reactions such as pruritus or swelling around the injection area and, more rarely, reports of local reactions to the udder after injections to the udder with penicillin derivates. The cows' udders became painful, swollen, reddened and in some cases the animals' temperature rose (to over 40 °C). Since the causality was assessed as "possible" in all cases, corresponding adjustments to the Product Information were formally requested. Five further reports concerned undesired residue from antibiotics in meat or milk after respecting the prescribed time limit following the cessation of treatment. It was only possible to establish a certain assocation to the product in one case of off-label administration (the product was administered twice instead of only once).

In 2009, a slight shift was observed regarding the other categories of medicines. Reactions in the QH (hormonal products) and QG category (urogenital system and sex hormones products) were the third and fourth most frequent reports received. For the QH category, the reason may be attributed to the launch of two new products in the months of May 2008 and June 2009. The latter product is a new application system using an active substance that had not been used in veterinary medicine before: from experience, such new authorisations lead to a higher number of reports since the risk profile of the new products is not well known by practising veterinarians. No reason for the increase in the reporting rate for QG category reports is identified at present. Less than ten reports were submitted for all other ATCvet product groups, with the exception of the redesignated category QZ***** (a highly heterogeneous group). For 18% of the groups, a causal association between the application and the reaction was assessed as "probable", and in 36% as "possible". For the remaining reports, there was either too little information available (38%) or an association was clearly ruled out (8%).

Interesting cases

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Cases worthy of mentioning include a cat with a high-grade lymphopenia and granulocytopenia with a regenerative left shift, four days following oral administration with chloramphenicol (assessed as “possible”), and deafness in an eight-year old Schnauzer after treatment with ear drops containing gentamicin (“possible”). In the latter case, the situation improved after two weeks but without full recovery. A further report stated the onset of myasthenia gravis in a German sheepdog after the administration of an NK1 blocker as an anti-emetic. The causal link could not be confirmed. To date, no similar reaction has been observed anywhere in the world, nor does it match the current safety profile of the active substance. Moreover, this race of dog is predisposed to this neurological disease. Finally, two reports were received regarding possible reactions to antiparasitics in humans administering the veterinary medications: in one case, a local irritation to an eye was observed, and in the other it was an accidental needle stick injury, without further consequences.

In addition to the reports on veterinary medicines authorised by Swissmedic, 912 reports on adverse reactions following veterinary vaccines were sent to the IVI (Institute for Virology and Immunophrophylaxis, Mittelhäusern, as the competent authorisation and monitoring authority). The overwhelming majority of the reports (866) concerned reactions following the vaccination of ruminants against bluetongue disease, within the framework of a campaign organised by the Swiss Confederations, and 46 reactions occurred after various other veterinary vaccinations of other species. At present, no further analysis of these reports is available.

Table 1: Reports received in 2009, categorised by type of animal

Type of animal	Number	% Total
Dog	61	46%
Cat	25	19%
Horse / donkey	6	4%
Cow / calf	30	23%
Sheep	2	1%
Pig	6	4%
Domestic an zoo animals	2	1%
Users	2	1%
Total	**134**	**100%**

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Table 2: **Reports received in 2009, by ATCvet code**

Category of medicines according to ATCvet	Number of reports (% of relevant total)
QA: Alimentary tract	7 (5%)
QB: Blood and blood forming organs	1 (1%)
QC: Cardiovascular system	3 (2%)
QD: Dermatologicals	1 (1%)
QG: Genito-urinary system and sex hormones	14 (10%)
QH: Hormonal preparations (except hormones and insulin derivatives)	17 (13%)
QJ: Anti-infectives	26 (19%)
QL: Antineoplastic and immunomodulating agents	1 (1%)
QM: Musculoskeletal system	4 (3%)
QN: Nervous system	6 (4%)
QP: Antiparasitics	40 (30%)
QS: Sensory organs	2 (1%)
QV: Various	1 (1%)
"QZ*": Redesignated products	10 (7%)
ALP registered products, animal care products, etc.	1 (1%)
Total	**134**

* *The QZ is fictitious but permits the specific grouping of reports of adverse drug reactions to redesignated products (i.e. not used for the authorised type of animal and / or indication)*

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V: Information regarding the safety of medicines - published on the Swissmedic website

11.06.2010	HPC: Risperdal Consta (risperidonum) *
04.06.2010	Rotarix® (oraler Rotavirus-Impfstoff) kann ohne Einschränkungen angewendet werden *
31.05.2010	HPC: Exelon Patch (Rivastigmin) – unsachgemässe Anwendung mit Risiko der Überdosierung *
20.05.2010	HPC: Avastin (Bevacizumab) HPC: Avastin (Bevacizumab) *
19.05.2010	HPC: Rapamune® (Sirolimus) *
21.04.2010	Swissmedic warnt vor folgenden illegal vertriebenen Schlankheitsmitteln *
16.04.2010	International Conference on counterfeit medical products paves the way to landmark convention aimed at protecting public health
08.04.2010	3. Haemovigilance Tagung (26. August 2010) *
30.03.2010	HPC: Wichtige Mitteilung zu Reductil® (Wirkstoff Sibutramin) – Sistierung der Zulassung, keine Neu- oder Wiederverschreibung bzw. Abgabe von Reductil® mehr gestattet *
25.03.2010	Swissmedic closes the formal investigation for contraceptives containing drospirenone
09.02.2010	Aristolochiaceae: Arzneimittel, die unter Verwendung von Pflanzen der Familie der Aristolochiaceae hergestellt werden *
09.02.2010	The trend continues: increase in imports of illegal medicines into Switzerland
21.12.2009	Swissmedic warns about dangerous substances in bodybuilding products
09.12.2009	Swissmedic informiert über Impfregister für Schwangere *
	Please find the complete list at the following web address: http://www.swissmedic.ch/aktuell/00003/index.html?lang=en

**** in German and French only***

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Report of a suspected adverse drug reaction (ADR)

► The ADR form can be filled in electronically:

MU101_20_001d_FO Meldung einer vermuteten unerwünschten Arzneimittelwirkung (UAW) [in German]
MU101_20_001f_FO Annonce d'effets indésirables suspectés d'un médicament (EI) [in French]

Contact

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We want to thank all colleagues for their contribution to the realisation of this Vigilance-Newsletter.

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